Review

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Restless legs syndrome

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Abstract. Ekbom K, Ulfberg J (Department of Neurology, Karolinska Institutet, Karolinska University Hospital, Huddinge, Sleep Disorders Center, Avesta Hospital, 14186 Stockholm, Sweden). Restless legs syndrome (Review). *J Intern Med* 2009; **266:** 419–431.

Restless legs syndrome (RLS) is a common neurological sensory-motor disorder that is characterized by intense restlessness and unpleasant creeping sensations deep inside the lower legs. Symptoms appear when the legs are at rest and are worst in the evening and at night. They force patients to keep moving their legs, and often to get out of bed and wander about. Periodic limb movements (PLMS) are also common during sleep amongst those suffering from RLS, and sleep efficiency is severely reduced. There are idiopathic as well as symptomatic forms of RLS, the latter being associated with e.g. pregnancy, iron deficiency and chronic renal failure. A family history of RLS is very common and pedigrees in these cases suggest an autosomal-dominant transmission with high penetrance. Genetic investigations have been performed in order to identify genes associated with RLS. Several loci have been found (on chromosomes 12q, 14q, 9p, 2q, 20p and 16p). Pathophysiology of RLS remains incompletely understood. However, advanced brain imaging studies and positive results of dopaminergic treatment suggest that RLS may be generated by dopamine dysfunction locally within the central nervous system. At present, there is a wide range of treatment options including levodopa, dopamine agonists, opioids, benzodiazepines, antiepileptic drugs and iron supplements.

Keywords: dopamine agonists, iron deficiency, periodic limb movements, restless legs syndrome, sleep.

Introduction

Restless legs syndrome (RLS) is a common neurological disorder that is characterized by an urge to move the legs (rarely also the arms) and peculiar, unpleasant sensations (paraesthesias) deep in the legs [1]. Sensations appear during periods of rest or inactivity, particularly in the evening and at night, and are typically relieved by movement. The paraesthesias may be exceedingly unpleasant and commonly give rise to severe sleep disturbances. Physical examination is generally normal, and with the exception of symptomatic secondary forms of the syndrome objective neurological signs are lacking. In >50% of cases there is a positive family history of RLS, and a number of molecular genetic investigations are now in progress. Symptoms of RLS are supposed to be generated centrally within the brain by local iron deficiency and dopaminergic dysfunction. Community surveys indicate that symptoms of RLS are found in about 5–10% of the general population, at least in Europe and North America. However, RLS is frequently undiagnosed and continued education of physicians and health personnel is important.

The purpose of this review is to describe the clinical features of RLS, consensus criteria for diagnosis and rating of severity of symptoms, RLS and sleep, recent progress of genetic research, views on pathophysiology and positive results of medical treatment, notably by some nonergoline dopamine agonists.

Historical notes

The term RLS was introduced by Karl-Axel Ekbom [2, 3]. He encountered a number of outpatients

complaining of peculiar and tormenting paraesthesias deep in their lower legs which he had never heard of before. In 1944 he reported on eight patients [4] and in 1945 he published his doctoral thesis, as a monograph [2], that was entitled 'Restless legs': 'a clinical study of a hitherto overlooked disease in the legs characterized by peculiar paraesthesia ('Anxietas tibiarum'), pain and weakness and occurring in two main forms, asthenia crurum paraesthetica and asthenia crurum dolorosa'.

In his first series of patients, Ekbom was able to collect 34 severe and 120 mild cases of the paraesthetic form of the disease, and 15 cases of the painful form. 'Restless legs' proved to be easily recognisable and was found to be very common, about 5% in a 'normal' population. Many sufferers had one or more close relatives with creeping sensations in their legs that in these cases suggested hereditary factors as an aetiological background. Ekbom also described RLS in pregnancy and later as a symptom of iron deficiency anaemia [3], in carcinoma, and in blood donors [5] (Fig. 1).

In the early literature there were only few, very brief descriptions that resembled RLS, but the symptoms seemed rather to have been regarded as a form of neurasthenia, hysteria or even as 'a common minor ailment' (for review see 2).

Fig. 1 Karl-Axel Ekbom (1907–1977).

In 1955, however, Macdonald Critchley [6] noted that the English physician and anatomist Sir Thomas Willis already in the 17th century had noted symptoms similar to RLS [7]. Karl Ekbom Jr and K.A. Ekbom [8] reported in 1974 on an early, previously overlooked, admirable description of symptoms being similar to restless legs, namely in Magnus Huss' extensive work of 1849 on chronic alcoholism [9]. And recently, another two most interesting descriptions of probable RLS and PLMS have been found in old French medical books [10] – published by Boissier de Sauvages in 1763 and Gilles de la Tourette in 1898.

Clinical features

Restless legs syndrome is characterized by unpleasant, creeping or crawling sensations deep within the lower legs, most commonly localised between the knees and ankles. The sensations may also be experienced in the thighs, and sometimes in the feet. They may be unilateral but are commonly bilateral and symmetrical. The arms can also be involved, but symptoms are usually more severe in the lower limbs.

The uncomfortable sensations are experienced only when the limbs are at rest for any length of time, and they are typically relieved by movement. Patients state that they are experiencing an almost irresistible urge to move the legs and they may have to be walking around in order to get relief. Symptoms of RLS are very severe e.g. during train journeys, flights, at the cinema or the theatre. They are also especially troublesome in the late evening when patients are getting into bed. Sensations may last for hours but may also persist, with interruptions, in some unfortunate sufferers, until 3, 4 or 5 AM Patients often have to get up and walk around many times to obtain relief. This form of coping behaviour has been named 'Night-walker's syndrome'. Loss of sleep is a serious consequence both to patients and their spouses.

Some are complaining about true pain which is felt as a dull ache of varying intensity, whilst the great majority of patients are suffering from creeping sensations only.

Restless legs syndrome is frequently associated with involuntary, rhythmic muscular jerks in the lower limbs: dorsiflexion or fanning of toes, flexion of ankles, knees and hips, so-called periodic limb movements (PLMS) [11, 12]. For further details see Section RLS and sleep.

Onset of RLS may occur from childhood to >80 years of age [13]. The natural clinical course varies widely but RLS is generally regarded as a chronic condition with a successive increase of symptoms.

Diagnostic criteria

Diagnosis of RLS is based primarily upon a careful clinical history and a detailed physical and neurological examination. There is yet no laboratory test that can confirm a diagnosis of RLS. Physical examination is usually normal, except for patients having a symptomatic secondary form of RLS or a comorbid condition.

Standardized clinical diagnostic criteria were introduced in 1995 by the International RLS Study Group (IRLSSG) [14] and later revised in 2002 by a workshop at the National Institutes of Health [13]. There are four essential criteria (Table 1) and all of them must be established to make a definite diagnosis of RLS. Furthermore, there are three supportive criteria (Table 2) that admittedly are not completely necessary for a diagnosis of RLS but they are definitely helpful in the differential diagnosis.

Table 2 Supportive clinical features of RLS (13)

Family history
Response to dopaminergic therapy
Periodic limb movements (during wakefulness or sleep)

Table 3 Differential diagnosis

Akathisia
Nocturnal leg cramps
Peripheral neuropathy
Lumbosacral radiculopathy
Painful legs and moving toes
Growing pains
Attention deficit hyperactivity disorder (ADHD)

Differential diagnosis. There are a few conditions that may resemble RLS but they do not fulfil the four essential diagnostic criteria for RLS (Table 3). Some of them are briefly commented here.

Akathisia is a common side-effect of neuroleptic drugs; patients are unable to sit still but they are feeling an inner general restlessness, which is in contrast to the strict localisation of paraesthesias in RLS. The diurnal rhythm of symptoms also differs: akathisia occurs during the day and does not disturb sleep.

The syndrome of *painful legs and moving toes* is characterized by involuntary, spontaneous flexion and

Table 1 Essential diagnostic criteria for RLS (13)

All of the following four criteria are necessary for a diagnosis
1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

extension of toes, mostly found to be secondary to trauma of the spinal cord, or the cauda equina, or by root lesions.

Rating of severity of symptoms

Restless legs syndrome is a subjective disorder and it may be difficult for examiners to evaluate exactly the severity of symptoms. However, IRLSSG has recently developed and validated a rating scale aiming at measuring the severity of symptoms [15]. It contains 10-items that are completed by patients themselves assessing the frequency and severity of RLS symptoms over the preceding week. Responses are graded from 0 to 4 (e.g. 0 = absence of symptoms, 4 = very severe symptoms), with a maximum total score of 40. The rating scale is especially utilized in evaluating effects of treatment.

Epidemiology

Restless legs syndrome is a disorder that hardly receives the attention it deserves. Two recent studies conducted in western Europe and in the United States clearly showed that RLS is greatly under-diagnosed and undertreated [16, 17]. The American patients' organisation 'Restless Legs Syndrome Foundation' has taken account of this and often reminds us that RLS is 'the most common disorder you have never heard of' (http://www.rls.org).

KA Ekbom recorded symptoms of RLS in 5.2% in a series of 503 'normal' subjects in Stockholm [2]. There was a slight female predominance.

In the last decade a large number of studies have been conducted into the occurrence of RLS, most of them being focused mainly on Caucasians in Northern Europe and the USA [18–21]. If age and gender differences are disregarded, the prevalence of RLS amongst Caucasians is approximately 5–15%. It is clearly indicated that the prevalence of RLS increases in relation to age, and that it is more prevalent amongst women [22–24]. Age at onset of RLS commonly occurs in the forties and fifties [13].

One of the most substantial and comprehensive population-based survey to date was conducted by Tison *et al.* [25] in a random sample of more than 10 000 French adults. Diagnosis was based on face-to-face home interviews addressing the issue of RLS. The one-year prevalence of RLS was estimated to be 8.5%, with a higher prevalence observed in women (10.8%) than in men (5.8%). This study clearly supports our opinion that RLS is a highly prevalent disorder [25].

Restless legs syndrome rates are low in some Asian populations [26, 27]. Based on the IRLSSG criteria, the prevalence of RLS in two samples in the Singapore-area was 0.6% and 0.1%, respectively [27].

Heredity – genetic aspects

In 1960 KA Ekbom [3] reported that 49 out of 112 unselected probands with severe, typical RLS knew of one or several close relatives with creeping sensations in their legs. RLS was also observed in a pair of monozygotic twins and their mother [28]. Since then familial RLS has been reported by several authors and at least 50% of patients do report a positive family history. RLS is 3–5 times greater amongst first-degree relatives of subjects suffering from RLS than in subjects without RLS [13], and pedigrees in most of these cases suggest an autosomal-dominant transmission with high penetrance. The possibility of anticipation – i.e. the disease starts earlier with each new generation – has been described in three large pedigrees of familial RLS [29, 30]. Variations in penetrance and anticipation suggest possible genetic heterogeneity [30].

Ten out of 12 monozygotic (MZ) twin pairs were reported to be concordant for RLS [31] which also indicates the importance of genetic influence. Desai *et al.* [32] evaluated RLS symptoms in 933 MZ pairs and 1004 dizygotic (DZ) pairs. Concordance rates were found to be 61% and 45% respectively. Heritability was estimated to be 54%.

A substantial number of investigations have been performed recently in order to identify genes associated

with RLS, and several loci (on chromosomes 12q, 14q, 9p, 2q, and 20p) have been reported [32–39]. Recently an autosomal-dominant locus for RLS in a French-Canadian pedigree has been found to map to chromosome 16p [39]. Genome-wide association studies have shown a positive association with sequence variants in or around specific genes on chromosomes 6p, 2p and 15q [34]. Amongst these genes the *MEIS1* gene has been considered as the leading common genetic risk factor identified so far [40]. *MEIS1* may have a function in the motor part of RLS and PLM [41, 42], and it has recently been suggested that reduced expression of the *MEIS1* gene, possibly through *cis*-regulatory element(s), may predispose to RLS [40]. There is also evidence of an association of variants in the NOS1 gene and RLS suggesting the involvement of the nitric oxide (NO)/arginine pathway in the pathogenesis [36]. Interestingly, PLMS have been genetically linked to a common variant of an intron of BTBD9 on chromosome 6p21 [43] that is associated with lower ferritin values.

Primary RLS

Both age and genes seem to play an important role for the susceptibility and clinical expression of RLS. Two subgroups of RLS phenotypes have been identified with regard to age of onset: primary (idiopathic) and secondary (symptomatic) RLS [44]. Patients with an onset of RLS before the age of 45 were found to have a significantly higher incidence of affected relatives compared with those who reported symptom onset later in life, i.e. >age 45 [44]. Thus, RLS with an early-onset and a positive family history of RLS strongly indicate genetic factors as an aetiological background. A short clinical history and onset after the age of 45, on the other hand, should raise a suspicion of a symptomatic form of RLS and indicates more detailed investigations.

Secondary RLS

Some RLS patients get their symptoms secondary to another disease process, a temporary disorder, or taking of substances/drugs. There are many causes of secondary restless legs.

Iron deficiency

There is at present an increasing bulk of data showing that RLS is common amongst subjects with iron deficiency. Nordlander [45] first reported on RLS and anaemia in three patients and also found that the creeping sensations ceased with intravenous iron therapy in 10 cases of iron deficiency anaemia and restless legs, often after a few injections only. KA Ekbom [46], reported on two male cases with malignancies (cancer in the urinary bladder and cancer in the gut). They were severely iron deficient and suffered also from RLS. Furthermore, he recorded low values for serum iron in 19 (25%) out of 77 unselected cases of RLS, and, in a series of unselected cases of iron deficiency anaemia (n = 50), he found RLS in 12 of them [16]. One study of 18 elderly patients with RLS and 18 matched control subjects revealed that serum levels of ferritin were reduced in the RLS patients compared with the control subjects [47].

In a Swedish survey consisting of 946 consecutive blood donors, 14.7% of the male blood donors and 24.7% of the female blood donors were affected by RLS [48]. The mean intake of iron amongst the blood donors after each blood donation was much lower than recommended.

Low-density lipoprotein-apheresis (LA) treatment induces a lack of iron. Tings *et al.* found that twelve out of 25 LA patients (48%) suffered from RLS [49]. Laboratory investigations showed that 11 of the 12 RLS patients had ferritin levels below or at the lower limit of the normal range.

In a recent Swedish survey amongst patients with polycytemia vera treated with venesectio (n = 34), who had iron deficiency but normal haemoglobin levels, as much as 29.6% of the patients were suffering from RLS [50].

Pregnancy

Restless legs syndrome is common during pregnancy, especially during the last trimester. The main cause of

this association is not well known. Deficiency of iron and vitamins, often seen in association with pregnancy, may be a major cause. Symptoms of RLS are usually temporary in nature, and most pregnant women find that their leg restlessness disappears soon after childbirth.

KA Ekbom was first to report that RLS was common during pregnancy: as many as 11.3% out of 486 pregnant women were found to suffer from RLS [2]. These data were in 1960 corroborated by Karl Ekbom Jr [51], who reported that 25 (12.4%) out of 202 pregnant women suffered from restless legs. The leg restlessness usually improved when those who were iron deficient were prescribed oral or i.v. iron therapy.

Manconi *et al.* reported that in a population of 642 pregnant women 26% were found to be affected by RLS during their pregnancy. RLS was strongly related to the third trimester of pregnancy [52].

Kidney disease

Callaghan was first to describe a relationship between RLS and end stage renal disease (ESRD), uraemia [53]. Prevalence of RLS symptoms ranges from 6.6% to 83% [54, 55]. Thus, many patients treated with dialysis due to uraemia, suffer problems with restless legs that are also difficult to manage. RLS occurs both before and after dialysis treatment but can be improved after renal transplantation [56].

Rheumatic disease

Restless legs syndrome may occur amongst those who suffer from joint and muscle diseases such as fibromyalgia and rheumatoid arthritis [57, 58]. However, in this area the literature is sparse, so it is not known how to explain a possible relationship.

Drugs

There are many examples of drugs which have the ability to provoke or exacerbate restless legs. According to Ondo, the most notable of these include antihistamines, dopamine antagonists (including many antinausea medications), mirtazapine, and possibly tricyclic antidepressants and serotonergic reuptake inhibitors [59, 60].

Pathophysiology of RLS

Dopamine

According to a commonly held view RLS may be due to dysfunction of dopamine cells in the nigro-striatal areas of the brain. Pharmacological studies have shown a dramatic improvement of RLS symptoms with the administration of levodopa, the precursor of dopamine, or with dopaminergic agonists acting on dopamine receptors in the brain.

Advanced brain imaging has shown decreased dopamine D2 receptor binding in the striatum of patients with RLS [1]. Hypoactive dopaminergic neurotransmission in RLS has recently been demonstrated by Cervenka *et al.* [61] and their results suggest that both striatal and extrastriatal brain regions are involved.

Iron is likely to be involved in this disease process. Iron is a necessary cofactor in the brain for the synthesis of dopamine and the regulation of dopamine receptors, and thus for the amount of dopamine available in the synapse. Iron and ferritin have been found to be abnormally low in the cerebrospinal fluid of RLS patients [62, 63]. Advanced brain imaging has also recently shown reduced iron stores in the striatum and red nucleus [64], being more marked for patients with an early-onset of RLS (<45 years) [65]. Moreover, nigral iron concentration was shown to be inversely correlated with severity of the disease.

It is hypothesized as well, that other substances for signal transmission in the brain, such as those inside the endogenous opioid system, may exert their effect by altering the dopamine function and may indirectly induce therapeutic effects for RLS [66].

RLS and sleep

Restless legs syndrome is a major cause of insomnia, and sleep disruption is a frequent complaint that

brings sufferers to consultation [67, 68]. In addition, sleep loss and fragmentation of sleep due to RLS has a major impact on health and daytime functioning [21–23, 69–71].

Periodic leg movements in sleep

More than 80% of RLS patients have involuntary muscular jerks in the lower limbs, periodic leg movements in sleep [11, 12, 72, 73]. They are typically recorded by electromyography (EMG) during polysomnography (Figs 2 and 3).

Periodic leg movements in sleep are often associated with increases in autonomic activity [74, 75]. There is a rise of blood pressure in PLMS as well.

The sleep structure of sleep in RLS sufferers may be impaired both by initiating and maintaining sleep, together with microarousals due to PLMS.

Daytime consequences of sleep disruption in RLS

Sleep debt in insomnia and RLS as well have widespread short-term and long-term consequences on health, mental state, productivity, safety and overall quality of life [76–80].

General consequences of sleep disruption in RLS

Depression is common in RLS patients and may be related to the chronic unremitting nature of symptoms, to the persistent sleep loss or to the underlying brain abnormalities that causes RLS [21, 81–83]. Treating depression in RLS patients may be difficult at times since some of the antidepressants may individually exacerbate RLS symptoms.

The most disturbing feature of RLS may be the social disruption caused by the need to decrease evening or late afternoon social or work engagements that

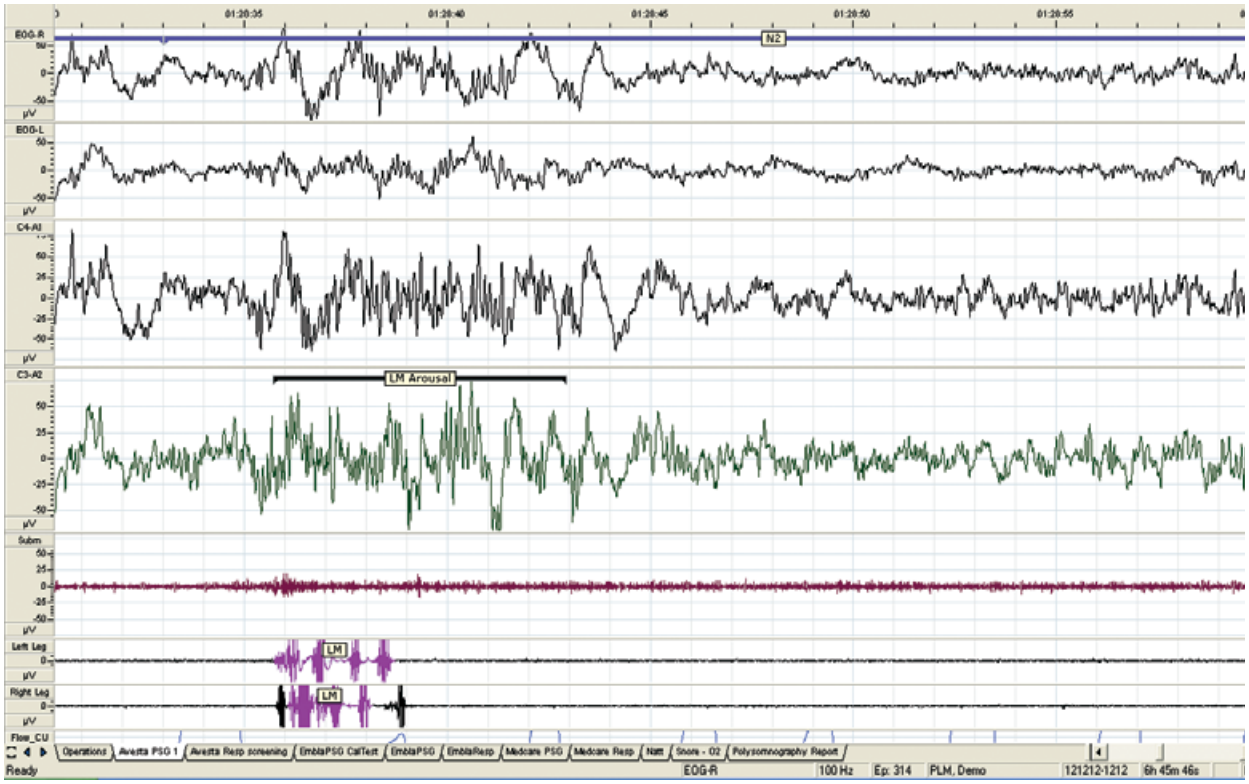

Fig. 2 A polysomnographic recording during 30 s. Leg movements in the bottom of the recording, leading to a microarouasal, seen in the upper part.

Fig. 3 Hooking up for a polysomnographic (PSG) recording.

involve inactivity. Theatre or board meetings or even social dinners can be very challenging to RLS patients [21, 22, 69]. Patients with RLS often experience difficulty in concentrating on daily tasks such as those demanded by their work. They may suffer from problems with short-term memory and some have severe learning difficulties [83].

Restless legs syndrome patients are more prone to headaches than healthy subjects, probably secondary to the sleep disturbances and sleep loss [21, 22, 84]. Headaches are similar to migraine in character, though with an element of tension-type headache [84]**.** RLS sufferers may wake in the morning with a headache; the headache may disappear during the morning, but can persist all day.

Restless legs syndrome may be linked to cardiovascular disease [21, 85]. Sleep disturbances, regardless of genesis, can have a negative effect on the cardiovascular system. Periodic limb movements during sleep induce rises in blood pressure, which may also be an underlying causal mechanism in this context [75].

Treatment

Treatment includes both nonpharmaceutical and pharmacological therapy, as well as treating the specific cause in patients of secondary RLS.

Treatment of secondary RLS

Iron deficiency is a common cause of secondary RLS, and it is necessary to assess iron storage in all cases of RLS. Serum ferritin is the best indicator of iron deficiency and iron treatment should be continued until serum levels of ferritin are higher than 50 μg/L [86, 87]. The cause of iron deficiency should of course be investigated. Serious diseases such as cancer of the gastrointestinal tract may first manifest itself as iron deficiency due to occult bleeding unnoticed otherwise.

When associated with kidney disease, there is generally no improvement of RLS under treatment with haemodialysis. These patients are amongst the worst cases of RLS to handle and they generally require pharmacological treatment. However, symptoms may improve after kidney transplantation [56].

In patients with neuropathy, RLS symptoms may improve by treatment of the primary condition. RLS is sometimes found in association with vitamin B12 and folic acid deficiency, especially in older individuals or in pregnant women. These patients should be treated with B12 or folic acid [88, 89].

Several drugs may trigger or worsen restless legs, and physicians should therefore look at the possibility that symptoms may be due to pharmacotherapy.

Treatment of primary RLS

Nonpharmacological treatment such as exercises during daytime and/or massage of legs and arms may be useful. However, in most patients who suffer from moderate or severe RLS symptoms there is need of pharmacological treatment.

Drugs used to treat RLS belong to many different pharmacological classes; the dopaminergic agents, opioids, benzodiazepines and antiepileptics.

Three nonergoline dopaminergic agonists are approved by Governmental Agencies to treat RLS; pramipexole, ropinirole and transdermal rotigotine. Other medications are useful but they are used off-label. Patients should realize that the treatment is life-long in most cases. Consequently, patients should take the lowest effective dosage to insure long-term efficacy.

Dopaminergic drugs

Levodopa. Levodopa was first given to RLS patients by Akpinar in Turkey in 1982 [90]. Subsequently, a series of short- and long-term controlled studies have confirmed that levodopa is effective to treat RLS and to suppress PLMS [91, 92].

A major limitation of levodopa therapy is the occurrence of morning rebound and afternoon augmentation of RLS symptomatology. Augmentation is a worsening of symptoms in late afternoon or in early evening. RLS symptoms occur earlier during the day to the point that it requires repeated administration of levodopa also during daytime. Several patients report that other previously unaffected parts of the body are progressively being involved such as the arms or the trunk. Augmentation was first reported by Allen and Earley and found to occur in >80% of RLS patients treated with levodopa, especially at a dosage exceeding 200 mg per night [93, 94]. Recently, a consensus conference arranged by the European RLS Study Group at the Max Planck Institute in Munich, Germany has agreed on new operational criteria for the clinical diagnosis of RLS augmentation [95]. Interestingly, it has been shown that low serum ferritin levels may enhance symptoms of augmentation [96].

Dopamine receptor agonists

Pramipexole and ropinirole are both found to be effective to treat symptoms of RLS and to suppress PLMS in RLS patients in large double-blind placebo-controlled clinical trials [97–102]. They are also efficacious in long-term treatment of RLS [103, 104]. Transdermal rotigotine (another nonergot dopamine receptor agonist) has recently shown to relieve both night-time and daytime symptoms of RLS in a randomized, double-blind, placebo-controlled trial comprising 458 patients [105].

Augmentation is seen in patients treated with pramipexole and ropinirole but at a lower rate than with levodopa [106]. Interestingly, there were no signs of augmentation by 24 h transdermal delivery of low-dose rotigotine [105].

Opioids

The therapeutic effect of opioids was already noted in the original description of restless legs-like symptoms by Willis [7]. Several studies have shown positive short-term and long-term effects of various opioids [106]. In severe cases opioids may be considered as a second-choice treatment after dopaminergic agents [107, 108]. A recent meta-analysis has focused on clinical trials with dopaminergic agents and opioids, two treatment modalities that are also involved in the placebo response [109]. There was a large placebo effect for primary outcome measures, which has important clinical and scientific implications.

Benzodiazepines and related medications

The benzodiazepines work mostly in improving sleep and have no effect on core symptoms of RLS. Thus they are no longer generally recommended as a specific treatment for RLS. Clonazepam is the best documented benzodiazepine in RLS [110].

Antiepileptics

Gabapentin has been reported to be efficacious in treating RLS [111]. Moreover, Happe *et al.* reported that gabapentin was as effective as ropinirole in reducing PLMS and improving sensorimotor symptoms in patients with idiopathic RLS [112]. A novel gabapentin prodrug, XP13512 1.200 mg taken once daily, has also been recently shown to improve RLS symptoms compared with placebo after 12 weeks of treatment [113].

Iron injections

In the literature, randomized, placebo-controlled trials on iron treatment in RLS are still few. However, Sloand *et al.* showed that iron dextran infused in patients with end stage renal disease decreased RLS symptoms significantly when compared with placebo but the efficacy persisted only for 2 weeks [114]. Moreover, Grote *et al.* have shown that iron sucrose given intravenous in RLS works in the very short and longer term [115], and recently, the first double-blind, placebo-controlled study, on oral iron given over a 12 week period in RLS patients with low-normal ferritin values, demonstrated an improvement of IRLS scores amongst those treated with iron [116].

Conclusion

Restless legs syndrome is a major cause of insomnia, and the structure of sleep of sufferers may be severely impaired. Sleep disruption has in consequence a great impact on health and daytime functioning of RLS patients. Despite the fact that RLS is a very common disorder it is frequently undiagnosed in primary care, and therefore inadequate therapy may be prescribed. Recent research has provided a better understanding into the pathophysiology. There is evidence that iron deficiency and local dopamine dysfunction centrally in the brain are important. A number of molecular neurogenetic investigations are in progress to identify the genetic background to familial cases of RLS, but additional neurophysiologic and functional brain imaging studies are also needed to explain some crucial pathologic mechanisms of the syndrome. There is a wide range of therapeutic options, and at present dopamine receptor agonists are the first choice in treating moderate to severe cases of RLS.

Conflict of interest statement

Karl Ekbom is a member of a RLS Medical Advisory Board for Boehringer-Ingelheim AB, Sweden.

Jan Ulfberg none.

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